Insulin detemir
Levemir®

Classification: Recombinant human insulin analog, long-acting

Description:
- Levemir® 10 mL vial, 100 Units/mL
- Levemir® FlexPen® 3mL, 100 Units/mL - discontinued September 2014
- Levemir® FlexTouch® 3mL, 100 Units/mL

Pharmacology: Acts via specific membrane-bound receptors on target tissues to regulate metabolism of carbohydrate, protein, and fats. Target organs include the liver, skeletal muscle, and adipose tissue.

Pharmacokinetics: [1]
Onset of action: 3-4 hours, Cmax 6-8 hours post-dose
Systemic bioavailability: 60%
Distribution: Vd: 0.1 L/kg
Protein binding: >98% (albumin)
Half-life elimination: 5-7 hours (dose dependent)
Excretion: Urine

Indications: For the treatment of type 1 diabetes mellitus and type 2 diabetes mellitus to improve glycemic control in adults and children (over the age of 2).

Dosage:
Initiation, Type I Diabetes
Approximately 1/3 of the total daily insulin requirement administered in 1-2 divided doses, a rapid or short acting pre-meal insulin should be used to complete the balance of the total daily insulin requirement. When administering once daily, the dose should be administered with the evening meal or at bedtime.

Initiation, Type II Diabetes, inadequately controlled on oral antidiabetic mediations
10 Units (or 0.1-0.2 Units/kg) administered once daily in the evening or at bedtime or divided into a twice daily regimen, separated by 12 hours.

Initiation, Type II Diabetes, inadequately controlled on a GLP-1 agonist
10 Units administered once daily in the evening.
Converting from other insulin therapies:

If changing from Lantus® (insulin glargine) to Levemir® (insulin detemir) the change can be done on a unit-to-unit basis.

If changing from NPH to insulin detemir, the change can be done on a unit-to-unit basis, but those with type 2 diabetes may require more Insulin detemir than NPH as observed in one trial.

Administration:
Subcutaneous route of administration. Do not administer intravenously or intramuscularly due to the risk of severe hypoglycemia. Inject into the thigh, abdominal wall, or upper arm; rotate injection sites within the same region to reduce the risk of lipodystrophy. Don't dilute or mix with other insulin or solution. Not for use in insulin pumps.

Storage:
Vial:
Unopened (unused) vial: Refrigerate [2-8°C (36-46°F)]. May be stored until expiration date on the container. If refrigeration is not possible, store at room temperature[<30°C (86°F)] and keep as cool as possible, for 42 days. Do not freeze. Protect from direct heat and light.
Opened vial: Refrigerate [2-8°C (36-46°F)] or store at room temperature [<30°C (86°F)]. Discard after 42 days. Do not freeze. Protect from direct heat and light.
Vial after initial use: Vials should be discarded 42 days after initial use whether refrigerated or unrefrigerated even if it still contains insulin.

FlexTouch®:
Unopened Flex Pens may be refrigerated and stored until expiration date on container.
After initial use, store at room temperature [<30°C (86°F)] NOT the refrigerator, for 42 days. Do not refrigerate or store with the needle in place after initial use. Protect from direct heat and light.

Contraindications:
Known hypersensitivity to insulin detemir or any of its excipients.

Precautions:
- Never share a FlexTouch® pen between patients.
- Hypoglycemia is the most common adverse reaction and when a GLP1 receptor agonist is use in combination, the dose of insulin detemir may need to be lowered or more carefully titrated to minimize this risk.
- Renal impairment: There were no differences in the pharmacokinetics of insulin detemir between those patients without diabetes and renal impairment and healthy volunteers. Although, some studies have shown increased circulating insulin concentrations in patients with renal impairment so careful monitoring of blood glucose and dose adjustment may be needed in renal impairment.

- Hepatic impairment: In those patients with severe hepatic dysfunction and without diabetes, lower systemic exposures to insulin detemir were observed compared to healthy volunteers. However, some studies with human insulin have shown an increase in circulating insulin concentrations in patients with hepatic dysfunction so careful monitoring of blood glucose and dose adjustment may be needed in hepatic impairment.
- Pregnancy: category B
- Nursing Mothers: it is unknown if insulin detemir is excreted in human milk but because many drugs are, including human insulin, use caution when administering insulin detemir to a nursing woman.
- Thiazolidinediones (TZDs), peroxisome proliferator-activated receptor (PPAR)-gamma agonists, when used in combination with insulin detemir can cause dose-dependent fluid retention, which may exacerbate or lead to heart failure.

Interactions:
Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia and may require close monitoring or insulin dose adjustment.

Hypoglycemia	Hyperglycemia
Fibrates	Corticosteroids
Disopyramide	Diuretics
Pentoxifylline	Sympathomimetic agents
Salicylates	Thyroid hormones
ACE-inhibitors	Progestogens, estrogens (OCs)
MAO inhibitors	Atypical antipsychotic medications
Sulfonamide antibiotics	Protease inhibitors
Fluoxetine	Danazol
Oral antidiabetic agents	Phenothiazine derivatives
Somatostatin analogs	Isoniazid
Pramlintide acetate	Niacin
Glucagon	Somatropin

Beta-blockers, clonidine, lithium salts, and alcohol may either increase or decrease the blood-glucose lowering effect of insulin.

The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

Adverse Reactions:
Adverse reactions reported with an incidence >5% in clinical trials included: hypoglycemia, upper respiratory tract infection, headache, pharyngitis, influenza-

like illness, abdominal pain, back pain, gastroenteritis, bronchitis, pyrexia, cough, viral infection, nausea, rhinitis, and vomiting.

Other potential adverse reactions include: lipodystrophy (can decrease risk by alternating injection sites), weight gain, peripheral edema, antibody production, and local and systemic allergic reactions.

Hospital costs:
Levemir 10mL vial $127.65, 3mL FlexTouch pen $190.95
Lantus 10mL vial $92.81, 3mL Solostar pen $139.22
NPH 10mL Novolin N $18.12, Humulin N $11.83, Humulin N 3mL pen $10.57

Levemir/Lantus Hospital Purchases (FY2015):
Levemir 10mL vial: Item Qty 163, Item Total $24,026.45
Lantus 10mL vial: Item Qty 1370, Item Total $189,830.73
Lantus 3mL Solostar pen: Item Qty 21, Item Total $4,573.56

Levemir/Lantus Living Centers Purchases (FY2015):
Levemir 10 mL vial: Item Qty 62, Item Total $12,600.06
Levemir 3mL FlexTouch pen: Item Qty 6, Item Total $2,004.78
Lantus 10 mL vial: Item Qty 769, Item Total $115,111.35
Lantus 3 mL Solostar pen: Item Qty 7, Item Total $1,304.83

Monitoring:
Glucose monitoring is essential for all patients. Make sure patients also know how to recognize signs and symptoms of hypoglycemia and hyperglycemia.

Changes in insulin strength, manufacturer, type of insulin product, or method of administration may result in the need for a change in the insulin dose or adjustment of concomitant anti-diabetic treatment.

The time course of action for insulin detemir may vary in different individuals or at different times in the same individual and is dependent on many conditions including local blood supply, local temperature and physical activity.

Efficacy:

<u>Insulin detemir vs. NPH</u>
A study by Hermansen and colleagues compared the efficacy and safety of insulin detemir to NPH insulin dosed twice daily in those with type 2 diabetes on oral medication and A1c 7.5-10% (n=476). Over 24 weeks insulin doses were titrated starting at 10 units per injection to a goal prebreakfast and predinner blood glucose of 108 mg/dL or less. This was an open-label protocol because insulin detemir is a clear solution and NPH is a cloudy suspension. At 24 weeks there was no significant difference in A1c reduction between products (-1.8% insulin detemir and -1.9% NPH) and both groups had a similar percentage of

participants achieving a goal of A1c 7% or less (70%). There did appear to be less hypoglycemia and less weight gain with insulin detemir than NPH. Subjects achieving A1c goal without hypoglycemia 26% with insulin detemir and 16% with NPH (p=0.008). Nocturnal hypoglycemia was reduced by 55% with insulin detemir (p=<0.001). Weight gain was 1.2 kg with insulin detemir and 2.8 kg with NPH (p< 0.001).[2]

In a randomized, open-label, active-control, 26 week study, the efficacy and safety of a basal-bolus insulin regimen with either insulin detemir or NPH insulin along with mealtime insulin aspart was evaluated in those with type 2 diabetes (n=505). Those receiving more than one basal insulin injection per day pretrial continued on twice-daily injections, all others received once daily injections. Significant reductions were seen in A1c and FPG for both types of insulin and were similar between groups. There was no difference in adverse events including risk of hypoglycemia or nocturnal hypoglycemia between the groups. There was less within-subject day-to-day variation in FBG with insulin detemir (p=0.021). There was also less weight gain with insulin detemir, 1kg, than with NPH, 1.8 kg (p=0.017).[3]

A 16 week, randomized, open-label, active control study compared the safety and efficacy of twice daily insulin detemir (either before breakfast and bedtime or at a 12 hour interval) compared to twice daily NPH in type 1 diabetes (n=408). Insulin aspart was administered before each meal. Fasting plasma blood glucose was lower with insulin detemir than NPH using both insulin detemir dosing intervals (detemir 12h vs. NPH, mean difference -1.5 mmol/l, p=0.004; detemir morning+bedtime vs. NPH, mean difference -2.3 mmol/l, p<0.001). A1c was lower in the pooled insulin detemir groups (mean difference -0.18% [-0.34 to -0.02], p=0.027). The risk of minor hypoglycemia was also lower in both insulin detemir groups compared to NPH (25% lower for 12 hour interval and 32% lower for morning+bedtime regimen); most of the difference was noted to be attributable to a much lower risk of nocturnal hypoglycemia. Within person between-day variation in self measured fasting blood glucose levels were lower in the insulin detemir groups (both p<0.001). There was more weight gain associated with the NPH group (0.86 kg) than the insulin detemir groups (0.02 kg 12 hour interval and 0.24 kg morning+bedtime regimen).[4]

<u>Insulin detemir vs. Insulin glargine</u>

A randomized 52 week, randomized, open-label, treat-to-target trial compared once or twice daily insulin detemir (a second insulin detemir morning dose was given if pre-dinner plasma glucose was >126 mg/dL after titrated on insulin detemir) with once daily insulin glargine when given as an add-on to glucose reducing drugs in insulin naïve type 2 diabetes (n=582). The percentage of patients who met their A1c goal of <7% in absence of symptomatic hypoglycemia was similar (33% insulin detemir, 35% insulin glargine). The rate of hypoglycemic events was comparable, 5.8 insulin detemir vs 6.2 insulin glargine. Weight gain was lower in the insulin detemir group (3 kg vs. 3.9 kg, p=0.01). Insulin detemir

had a higher rate of injection site reactions (4.5% vs 1.4%). Mean daily insulin detemir dose was higher (0.78 U/kg) compared to insulin glargine (0.44 U/kg). [5]

In a 26 week, open-label, parallel-group trial, 320 adults with type 1 diabetes were randomized to either twice-daily insulin detemir (given in the morning and at bedtime) or once-daily insulin glargine (given at bedtime). Insulin aspart was given prior to each meal. The objective of this study was to compare the risk of hypoglycemia and glycemic control of these two treatments. There was no significant difference in A1c between treatment groups (both 8.2%) at the study endpoint. Insulin detemir has a slightly higher fasting plasma glucose (7.7 mmol/L) than insulin glargine (7.0 mmol/L) at endpoint ($p<0.001$). Predinner plasma glucose was less with insulin detemir (2.6 mmol/L) compared to insulin glargine (2.9 mmol/L), $p=0.049$; however, there was no significant difference in prebreakfast, prelunch, or overall values. The overall risk of hypoglycemia was similar between the groups; however, the risk of severe hypoglycemia was 72% lower and the risk of nocturnal hypoglycemia was 32% lower with insulin detemir compared with insulin glargine ($p=<0.05$). Weight gain between the groups was not significant (0.52 kg insulin detemir vs. 0.96 kg insulin glargine, $p=0.193$).[6]

A Cochrane review was conducted comparing insulin determir with insulin glargine in patients with type 2 diabetes mellitus and examined four trials lasting 24 to 52 weeks (n=2250). All four studies dosed insulin glargine once-daily in the evening. Three studies dosed insulin detemir once-daily in the evening with the option of an additional morning dose whereas the last study initiated twice-daily dosing. At the end of the trial for the three aforementioned studies, 13.6% to 57.2% of the randomized patients were injecting insulin detemir twice-daily. There was no significant difference between treatment groups for glycemic control, which was measured by A1C equal to or less than 7%, with or without hypoglycemia. There were no significant differences on occurrence of nocturnal and severe hypoglycemia between treatment groups. Although, there was a lower daily basal insulin dose necessary with insulin glargine. In addition, in 24-hour profiles of the two insulin analogs, there was no significant difference in the variability of glucose or FPG values. Less weight gain was seen with insulin detemir (one study showed a 0.9 kg difference) whereas a lower amount of injection site reactions were seen with insulin glargine (1.8% patients treated with insulin detemir versus 0.4% treated with insulin glargine). Lastly, one of the studies reported no significant differences on quality of life between the two randomized groups.[7]

Conclusions:

Current studies show insulin detemir to be effective in managing type 1 and 2 diabetes. Most studies evaluating insulin detemir compared to NPH or insulin glargine show similar reductions in A1c and fasting plasma glucose values; however, in order to achieve these similar rates, some studies have indicated a higher total daily insulin dose/kg was necessary for insulin detemir than the other insulins. The Rosenstock study reported a mean daily insulin detemir dose was

higher (0.78 U/kg) compared to insulin glargine (0.44 U/kg). That means in a 70 kg person, the cost per day (using the DSHS prices of $127.65per 10 mL vial of detemir and $92.81per 10 mL vial of glargine) of detemir comes out to be roughly $6.97 per day versus $2.86for glargine. Compared to insulin glargine and NPH, most comparator trials indicate insulin detemir causes slightly less weight gain. Insulin detemir can be dosed once or twice daily. Some studies have shown lower rates of hypoglycemia and nocturnal hypoglycemia with insulin detemir than NPH or insulin glargine; however, most of the information on lower risk of hypoglycemia comes from twice daily insulin detemir dosing vs. once daily insulin detemir dosing. Insulin detemir was also found to have a higher rate of injection site reactions compared to insulin glargine. Insulin detemir does not appear to have a significant advantage over other currently available formulary options aside from a slight decrease in potential weight gain as well as possible lower risk of hypoglycemia and nocturnal hypoglycemia when dosed twice daily. Although, when taking into account the 2015 fiscal year hospital and living centers purchases, insulin detemir is being currently being purchased by state hospitals, albeit the item quantity for detemir was 1207 less than glargine. Therefore, insulin detemir should be added to the formulary but it would not be the preferred product due to higher cost.

Formulary Recommendation:
Recommended for addition to the formulary as a reserve use drug for those unable to tolerate insulin glargine.

References:

1. Levemir® Package Insert. Plainsboro, NJ. Novo Nordisk. 2015.

2. Hermansen K, Davies M, Derezinski T, et al. A 26-Week, Randomized, Parallel, Treat-to Target Trial Comparing Insulin detemir with NPH Insulin as Add-On Therapy to Oral Glucose-Lowering Drugs in Insulin Naïve People With Type 2 Diabetes. Diabetes Care 2006; 29:1269-1274.

3. Haak T, Tiengo A, Draeger E, et al. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. Diabetes, Obesity and Metabolism 2005; 56-64.

4. Home P, Bartley P, Russell-Jones D, et al. Insulin detemir offers improved glycemic control compared with NPH in people with type 1 diabetes. Diabetes Care 2004; 27(5):1081-1087.

5. Rosenstock J, Davies M, Home PD, et al. A randomized, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin naïve people with type 2 diabetes. Diabetologia 2008; 51:408-416.

6. Pieber TR, Treichel H, Hompesch B, et al. Comparison of insulin detemir and insulin glargine in subjects with Type 1 diabetes using intensive insulin therapy. Diabetic Medicine 2007; 24:635-642.

7. Swinnen Sg, Simon AC, Holleman F, et al. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. Cochrane Database syst Rev. 2011 Jul 6;(7):CD006383.

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